Olaparib as maintenance therapy in patients with BRCA 1–2 mutated recurrent platinum sensitive ovarian cancer: Real world data and post progression outcome

TITLE: Olaparib as maintenance therapy in patients with BRCA 1-2 mutated recurrent platinum sensitive ovarian cancer. A real world experience from the MITO group.

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Abstract

Objectives: Olaparib is approved as maintenance therapy in patients with BRCA mutated platinum sensitive (PS) recurrent ovarian cancer (OC) after response to last platinum-based therapy. Few data are available regarding the use out of the registration trials and on response to further treatments after progression.

Materials ad methods: In this non interventional, retrospective study, patients treated with olaparib in 13 centers, according to the label, have been collected and analyzed. Primary objectives of the study is to describe effectiveness and safety of olaparib in a real world setting with a focus on post progression treatments and response.

Results: 234 patients were analyzed. All patients were BRCA mutated and most of them had germline mutations. Around 50% of the patients received olaparib after 3 or more lines of platinum-based chemotherapy achieving a radiologic complete (CR) or partial response. 12.4% patients with stable disease were also included. Median PFS was 14.7 months (95% CI:12.6-18), with statistically longer PFS in patients with normal serum Ca125 at baseline, a CR after last platinum based therapy and that received olaparib after second platinum-based therapy. Median OS was not reached. Most frequent G3-G4 toxicity was anaemia (6%) with dose discontinuation and dose reduction in 11 (4.7%) and 49 (20.9%) of cases, respectively. Among 66 patients receiving further treatment after olaparib progression and evaluable for response, ORR was 22.2, 11.1% and 9.5% in patients with Platinum Free interval (PFI) of more than 12 months, between 6 and 12 months and less than 6 months, respectively.

Conclusions: Olaparib is effective and safe in real world setting. Data on post-progression treatments seem to suggest cross resistance with chemotherapy and need to be confirmed in larger studies because of the potential importance in clinical practice decisions.

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Introduction

Ovarian Cancer (OC) is the most lethal gynecological malignancy worldwide [1, 2]. Indeed, it is frequently diagnosed at an advanced stage and despite optimal debulking surgery and platinum based chemotherapy, about 70% of patients relapse [3]. Recurrent patients can be roughly divided in those that are not candidate to receive a platinum rechallenge and those ~~seplatinum sensitive (PS),~~that are candidate to receive platinum again [1, 4-6].

In the last years, new knowledge on OC biology showed that almost half of the High-Grade Ovarian Cancer shows an alteration of Homologous recombination (HR) that is a high fidelity DSBs DNA repair mechanism, active during cell replication [7, 8]. These alterations lead to HR Deficiency (HRD), causing a less preserved DNA integrity and a higher response to DNA damaging agents like platinum compounds [9]. Among these alterations, BRCA1 and 2 mutations account for 22.6% of mutations in HGSOC~~and are related to increased risk of breast cancer and OC and a younger age at diagnosis, with 2/3 present at germline level and 1/3 somatic.~~ The patients carrying these mutations are highly responsive to platinum and this biological characteristics have been exploited therapeutically with the use of PolyADP Ribose Polymerase Inhibitors (PARPIs), that historically act with a synthetic lethal mechanism, leading HRD cells to apoptosis [10, 11]. ~~Indeed they inhibit PARPs, a family of enzymes that repair DNA Single strand Break (SSB) via Base Excision Repair (BER) and promote a conservative DNA repair facilitatingHR and inhibiting Non Homologous End Joining (NHEJ), a less conservative mechanism of repair~~[12, 13]. *In vitro* studies shows that BRCA1/2 mutated cell lines are really sensitive to cytotoxic activity of PARPIs and clinical trials confirmed that greatest benefit from PARPis is displayed in BRCA1/2 mutated patients, although an interesting activity was seen also in BRCA wild type OCs [12, 14].

Among these drugs, olaparib was the first in class drug to be developed and approved in OC. Olaparib is an oral inhibitor of PARP 1, PARP2 and PARP 3 [15, 16] that has been approved by EMA in 2014 as maintenance for patients with relapsed, platinum sensitive (with interval between last dose of platinum derivatives and progression longer than 6 months) BRCA-mutated (germline and/or somatic) HGSOC with complete or partial response (CR/PR) to last platinum-based chemotherapy [17]. This approval was based on Study 19, a randomized, placebo controlled phase II trial [18]~~. In this study 265 patients with PS recurrent~~

~~OC in response to last platinum based chemotherapy were randomized to receive Olaparib 400 mg twice a day or placebo as maintenance therapy. This study showed a significantly longer PFS for experimental arm (8.4 vs 4.8 months with HR of 0.35 P<0.001) with a greater benefit in BRCA (germline and somatic) mutated subgroup (11.2 vs 4.3 months HR 0.18 P<0.0001) and a trend toward a benefit in OS, with 15 patients receiving the drug for over 6 years~~[14, 18-20]~~Study 19results~~ that was confirmed by ~~were confirmed by the~~and SOLO2 trial, an international, multicentre, phase III randomized, double blind, placebo controlled trial, ~~that enrolled 295 BRCA mutated recurrent OC patients~~[21]. In this latter trial patients receiving olaparib maintenance therapy achieved an improvement~~These patients, after response to last platinum based chemotherapy, were randomized 2:1 to Olaparibin a new formulation (300 mg tablets, twice daily) or placebo until toxicity or progression. Primary endpoint was reached with an improvement~~ of 13.6 months in PFS (19.1 *vs* 5.5 months in placebo arms, HR 0·30 p<0·0001) [21, 22].

In both Study 19 and SOLO2 trials olaparib showed a safe profile, being the most frequent adverse events nausea, fatigue, vomiting and diarrhea, above all Grade (G) 1-2 and the most frequent G3-G4 toxicity anemia (18%). Treatment compliance was high with around 20% of the patients decreasing the dose due to toxicity [21].

Although these results have modified clinical practice in this setting, real world data on the use of PARPis are scarce, with short follow-up and small study populations [23-25], so there is the need to evaluate effectiveness ~~efficacy~~and safety of olaparib in a real world setting, ~~to understand if the results obtained in the selected patients included in the trials can be generalized to a wider and less selected population and, particularly if compliance to treatment is preserved also in everyday clinical practice~~[26, 27]. Moreover,we have few data in the literature on post progression treatment and response.

MITO therefore has designed a multicentre non interventional retrospective study that analyzed data from patients treated with olaparib in the general clinical practice, with the aim to describe effectiveness and safety data of olaparib in a real life setting, with a focus on post progression treatment and outcome.

Materials and methods

This is a non interventional, retrospective study conducted in 13 MITO (Multicenter Italian Trials in Ovarian cancer and gynecologic malignancies) centers. The study has been approved by the ethical committee.

Archival data from consecutive patients treated with olaparib (400 mg, capsule formulation) according to the EMA labelfrom September 1st 2015 up to 31 May 2019 have been collected by the centers, centralized in the coordinating institution(Istituto Nazionale per la Cura dei Tumori IRCCS Fondazione "G. Pascale" Napoli) and analyzed. Patients included in clinical trials were excluded.

Primary objectives of the study is to describe effectiveness and safety of olaparib in a real world setting. Effectiveness of olaparib maintenance treatment was described in terms of Overall Response Rate (ORR) according to RECIST 1.1 [28], Progression Free Survival (PFS), and Overall Survival (OS). Incidence of Adverse events (AEs), as well as dose reductions due to AEs were recorded. Also, post progression treatment and response were recorded and analyzed in all the patients experiencing a progression during olaparib therapy.

Disease assessment was performed according to routine practice (every 3 months) and RECIST 1.1 response was calculated locally. No central review was performed.

Centers reported all AEs records, graded according to Common Terminology Criteria for Adverse events (CTCAE) version 5.0 [29].

Statistical analysis

Baseline characteristics were analyzed according to descriptive statistics. Continuous variables were described with median values and interquartile range; categorical variables were described in terms of absolute numbers and proportion over the total number of patients analyzed.

PFS defined as time from first day of olaparib administration until disease progression (defined as objective radiological disease progression using modified RECIST version 1.1 or clinical progression) or death. Patients who did not experience disease progression were censored on the date of the last follow-up visit. OS was defined from first day of olaparib administration to death for any cause or the last follow up visit for living patients. PFS and OS curves were described according to the Kaplan Meier product-limit method and

compared with adjusted Log Rank test. Median follow-up was calculated according to the inverted Kaplan Meier technique [30].

HR and 95% confidence interval (CIs) were estimate with multivariable Cox models including number of lines, stage, residual disease at primary surgery, previous treatment with bevacizumab, age (continuous), mutational status, ECOG and RECIST1.1 Response [31].

All the analyses were performed with STATA 14 MP (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.)

Results

Patients characteristics

Two hundreds and thirty-four patients were enrolled from 13 centers, treated from 13 June 2015 to 31 May 2019, cutoff date. Main characteristics of patients are showed in Table 1. Median age at diagnosis was 53,2 (IQR 46.6-59.4) years. About 71% of patients had an ECOG PS of 0,while 24.8% of patients had an ECOG PS of 1 or 2; in 38,5%of the patients comorbidities were reported. All patients were BRCA mutated. About 70% of patients had a BRCA1 mutation, while 29.9% carried a BRCA 2 mutation, 1 patient was both BRCA 1 and BRCA 2 mutated. Most patients had germline BRCA mutation while 6.0% of patients had somatic mutation. Only 42.7% of the patients had familiar history of ovarian or breast cancer and 15.4% of the cases had personal history of breast cancer.

Most patients (75.2%) had FIGO stage III OC at diagnosis, 91.9% of patients had an HGSOC histology, while the remaining patients had OC with other subtypes (above all high grade endometrioid cancer). More than half patients were optimally debulked at diagnosis (60.3%) and almost all patients were treated with a platinum doublet at diagnosis, being Carboplatin-Paclitaxel three weekly (48.3%) and Carboplatin-Paclitaxel three weekly with Bevacizumab (41.5%) the most administered regimens. Median initial Platinum Free Interval (time between the last cycle of platinum during first line and evidence of disease progression, PFI)~~after first line~~ was18 (IQR 12-27.5) months.

Patient characteristics before olaparib administration are summarized in table 2.

Patients that received olaparib had a median PFI after last platinum therapy of 9.0 (5.0-14.2) months. In 47.4% of the patients olaparib was administered after second platinum-based line. Nevertheless, 41.0% and 11.5% of patients received olaparib after 3 and 4 or more lines of platinum based chemotherapy, respectively. As for platinum based regimens, 86.3% of patients received a platinum doublet before maintenance therapy with olaparib, while 10.3% of the patients received a platinum derivative alone. Most patients had a radiologic PR (45.3%) or CR (38.9%) to last platinum based therapy, but 12.4% patients received olaparib after a Stable disease (SD).

184

185 *Treatment effectiveness*

186 With a median follow up of 15.5 months (95% CI 13.0-18.2), 234 patients received at least one dose of
187 olaparib. One hundred and twenty three patients were evaluable for radiologic response with 35 CR, 22 PR
188 and an ORR of 46.3%. Among patients with SD after last platinum therapy, six patients out of 29 achieved a
189 PR or CR per RECIST (20.7%). At time of analysis 150 patients have received olaparib for at least 6 months,
190 85 patients for at least 12 months and 35 patients treated for more than 2 years. About 50% of the patients
191 are still on treatment at time of the analysis.

192 With 116 events recorded, median PFS (mPFS) was 14.7 months (95% CI:12.60-18.03) (Figure 1).

193 Explorative subgroups analysis have been performed (see Table 3 and Figure 2). Median PFS was
194 statistically longer in patients with normal serum Ca125 at baseline (cut off 35 UI/ml) (25.5 months vs7.9
195 months with and an adjusted HR of 2.5 (95% CI 1.5-4.3, p: 0.001). Also patients receiving olaparib after
196 second platinum based had longer PFS compared to those treated in third and in later lines, with a mPFS of
197 16.6, 15.5 and 8.2 months for patients treated in 2nd line, 3rd line and later lines [adjusted HR of 1.9 (95%
198 CI 1.1-3.5, p:0.031) and of 2.5 (95% CI 1.3-4.8, p: 0.004), respectively]. Patients achieving a CR after last
199 platinum based therapy had a statistically significant longer mPFS if compared with patients achieving a PR
200 [(33.4 vs 10.4 months), HR of 3.0 (95% CI 1.6-5.8 p:0.001)], and a SD [(33.4 vs 9.2 months), HR of 2.7
201 (95%CI 1.2-6.1, p: 0.017)], respectively.

202 No difference in mPFS was recorded according to stage and residual disease at primary surgery,
203 administration of Bevacizumab during first line treatment, ECOG PS, BRCA 1 or 2 status, age or previous
204 familiar history of BC or OC. Median OS was not reached with only 32 events recorded (Figure 1).

205 *Dose adjustment and safety*

206 Two hundred and twenty nine patients received olaparib at the recommended starting dose of 400 mg b.i.d,
207 while 5 patients received the drug at a reduced dose of 200 mg b.i.d since the beginning. Median treatment
208 discontinuation was 11.6 months and reason for discontinuation was progression or death in 108 patients

(46.2%) and toxicity in 11 (4.7%) of cases. Dose adjustment was required in 49 (20.9%) patients above all for hematologic toxicities (anaemia in 33% of dose adjustments). Most frequently recorded toxicities were nausea (35.7%) anaemia (35.7%) and fatigue (35.1%), above all G1 or 2. Most frequent G3-G4 toxicity was anaemia (6%) (See Table 4 for all G3-G4 AEs).

There was no statistical difference in incidence of G3-G4 AEs according to interval between last cycle of chemotherapy and first dose of olaparib maintenance therapy or according to line of therapy (2nd line versus later line). There was no statistical difference in PFS between patients treated with recommended dose of 400 mg bid and patients requiring a dose reduction (or treated with reduced dose since the beginning).

Post progression treatments

Among 110 patients with progressive disease, 2 patients received endocrine therapy and 86 patients received at least one further line of chemotherapy. Among these women, 25 had a PFI of more than 12 months, 39 a PFI between 6 and 12 months and 24 a PFI of less than 6 months. Sixty-six patients were evaluable for response.

Response to post progression therapy is reported in Table 5. Eighteen (72%) patients with PFI of more than 12 month wereevaluable for response. Among these, 14 cases were treated with a platinum based therapy, with 13 patients receiving platinum doublet and 1 patients receiving carboplatin as single agent. ORR was 22.2% (1 CR; 3 RP; 7 SD, 7 PD).

Among patients with PFI between 6 and 12 months, the most frequent treatment was a rechallenge with platinum derivatives (35.9%, 14 patients), although 64.1% of patients received other therapies (12 patients received trabectedin alone in the setting of MITO23 trial, 4 patients received trabectedin in combination with liposomal pegilated doxorubicin). Among patients of this group evaluable for response, ORR was 11.1% (3 PR, 8SD; 16 PD).

232 Patients with PFI of less than 6 months received a monotherapy in the majority of the cases, being weekly
233 paclitaxel and trabectedin (9 and 4 patients respectively) the most frequently administered regimens. ORR
234 was 9.5% (1 CR and 1 PR) with a PD in 76.2% of the cases.

Discussion

This study analyzed 234 BRCA mutated recurrent patients with OC treated with olaparib as maintenance after a platinum based chemotherapy. Median PFS was 14.7 months (95% CI:12.6-18), that is comparable to the data of the registration trials, and a safe toxicity profile was also observed in this real life setting. Interestingly patients progressed after olaparib and that were treated with chemotherapy had unexpected poor response rate of 22.2, 11.1% and 9.5% in patients with a PFI of more than 12 months, between 6 and 12 months and less than 6 months, respectively.

Our study is the first work that reports data on post progression treatment and response after maintenance therapy with olaparib, suggesting that RR is lower than expected. With the intrinsic limit of its retrospective nature, this finding shed a light on one of the upcoming urgent clinical research need, being olaparib maintenance therapy, a new standard also in first line treatment.

We currently know that olaparib and other PARPi maintenance therapy improved PFS in registration randomized clinical trials in recurrent patients treated as maintenance after response to platinum based chemotherapy. Namely, in Study 19 phase II trial patients receiving olaparib 400 mg twice a day as maintenance therapy had a longer PFS (8.4 vs 4.8 months in placebo arm with HR of 0.35 P<0.001) with a greater benefit in BRCA (germline and somatic) mutated subgroup (11.2 vs 4.3 months HR 0.18 P<0.0001) and a trend toward a benefit in OS, [14, 18-20]. These data were later confirmed by the SOLO2 trial [21], in which BRCA mutated patients receiving olaparib (300 mg tablets, twice daily) maintenance therapy had significant benefit in PFS [21, 22]. After these results olaparib has been rapidly introduced in everyday practice, modifying treatment algorithms. Nevertheless in SOLO2 and Study 19 trial, as usually in all registration trials [14, 21], olaparib was administered to very selected patients from highly experienced providers with very straight rules, timelines and schedules per protocol. This improved PFS obtained in an ideal setting needs external validity in a less selected population.

Real world studies could be useful as *a "measure in understanding health care data collected under real life practice circumstances*" (European Forum "Relative Effectiveness" Working group) [32], and the results can help defining if drugs are effective also in real world setting.~~with heterogeneous populations in centers with~~

~~representative providers and outside straight rules of protocols. Moreover defining cost-effectiveness of new drugs could be easier if results from clinical trials are straightened by real world studies.~~

Few results from olaparib real world use have been reported, with short follow up [25] or small population [33], lacking essential clinical information like BRCA status [23] and focusing above all on safety.

This study is the first real world experience published *in extenso* including only BRCA mutated patients with OC treated according to EMA label with olaparib maintenance therapy after platinum based therapy. Indeed, as a result of a real world setting, 24.8% of our patients had ad ECOG PS of more than 0 and 38.5% had registered comorbidities. Our study, as in the registration trials, includes patients receiving olaparib after at least second line of platinum based therapy, with several cases treated after 3 or 4 lines of chemotherapy.

In our study median PFS was 14.7 months and ~~was 14.7 months. This result is~~ is slightly lower than in the SOLO2 trial (19.3 months) [21] (Table 6). This difference could be explained by the less selected population including also some cases treated after a SD at the last platinum received.~~Subgroup analyses identified patients with a longer PFS providing information that could be useful in patient consenting clarifying them the expectations of patients in this setting.~~ Indeed our analyses suggest that patients achieving a CR to last platinum therapy and with low Ca 125 at baseline, have a better PFS when treated with olaparib~~in terms of PFS~~, identifying a population that probably includes long responders to olaparib. This results are consistent with data published by other groups [34, 35], although the prognostic role of Ca 125 has never been reported in this setting and, if confirmed, could be an easy tool for clinicians to predict duration of treatment with olaparib. Ca 125 data need also to be taken into account when indirectly comparing efficacy in trials with different PARPi; in fact some registration trials included only patients with normalized Ca 125 [36]. Although SOLO2 has demonstrated that the benefit of olaparib is evident independently from the number of previous line, we show that patients treated after 3 or 4 chemotherapy lines have significantly shorter PFS. We believe that this information can be useful for clinicians and patients when deciding the therapy, particularly where alternative regimens are available.

In our series a small subgroup of patients with SD to last platinum based therapy was treated with olaparib achieving a ORR of 20.7%. Although this group of patients is small these data suggested an interesting activity also in this setting.

As for safety, data on AEs and dose reduction do not differ from results of SOLO 2 trial, confirming that olaparib is a manageable drug also in everyday practice in a less fit population. Moreover dose reduction was recorded in 20.9% of patients (a result similar to SOLO2 trial) and does not seems to worsen outcome in our population.

We believe that an interesting data from our real world study is the post progression treatment efficacy in this setting. In fact, we found that ORR to chemotherapy in patients evaluable for response is lower than expected according to the PFI [37, 38]. In particular we found an ORR of only 22.2% in patients progressed after a longer olaparib therapy, treated with platinum again after a PFI of more than 12 months. Due to the fact that about 50% of the patients are still on treatment, these data will need further update and have to be considered preliminary. Also, the retrospective nature of the trial that is based on self-reported response rate require that our conclusions need to be confirmed. Nonetheless, we believe that this observation will prompt further research in the field exploring cross resistance between PARPi and chemo, and if confirmed in further studies, might have a significant impact on our clinical decisions.

The cross resistance suggested in our study has been demonstrated in preclinical models [39], and could play a role also in the clinic. In fact, although in the registration trials it has been shown that the time to second progression is prolonged in the arms treated with PARPis, the response to chemotherapy has not been described and data may be important in the selection of the drugs to be used in clinical practice, with more sequence studies needed in the future. These data may have also have a potential impact on the strategy of PARPIs after PARPIs that is currently under investigation (NCT03106987, OReO study).

Our results seems to be~~are in~~ contrast with a retrospective study published by Kaye and colleagues [40] that showed an ORR of 36% in 67 patients that progressed to olaparib and were treated with chemotherapy and an ORR of 40% in 48 patients receiving a platinum derivative. Nevertheless they analyzed both platinum sensitive and resistant patients that received olaparib not only as maintenance therapy but also as monotherapy, with a median interval from start of olaparib and subsequent line of only 7.4 months making the comparison between the two studies difficult due to different populations[40].

In conclusion we found that olaparib given in a real life setting of less selected patients is active and well tolerated. Patients in CR and with normal Ca125 have longer PFS. Nevertheless ~~Further studies will be needed to clarify if these easy clinical parameters can help to identify the population of long responders cases~~

~~that have been described with all the PARPi.~~we found lower response rates than expected according to PFI in patients treated with chemotherapy after olaparib progression. These data, although provocative, need to be confirmed in further studies investigating this important aspect also in the first line scenario, and adding translational studies evaluating the biological meaning of cross resistance between PARPi and chemotherapy.

Author contributions

Dr. Cecere and Dr. Pignata are responsible for study concept and study design. Dr. Pignata is responsible for Funding acquisition. Dr. Arenare and Dr, Giannone are responsible for quality control of data and algorithms. Dr. Arenare, Dr. Cecere and Dr. Giannone are responsible for data analysis and interpretation. Statistical analysis were performed by Dr. Arenare. Dr. Cecere, Dr. Giannone and Dr. Pignata prepared and edited the manuscript. All authors acquired data and reviewed manuscript.

Conflict of interest statement

Dr. Cecere reports honoraria from AstraZeneca, Tesaro and Pharmamar, outside the submitted work. Dr. Giannone reports grants from Roche, outside the submitted work. Dr. Salutari has been part of advisory boards of AstraZeneca, PharmaMar, Tesaro, MSD, outside the submitted work. Dr. Lorusso has been part of advisory boards and received institutional support for research from Immunogen, Genmab, Pharmamar, Clovis, Tesaro, Merck, AstraZeneca, outside the submitted work. Dr. Bergamini reports honoraria from AstraZeneca outside the submitted work. Dr. Orditura reports personal fees from Tesaro, outside the submitted work. Dr. Valabrega reports speaking honoraria from AstraZeneca, Tesaro, Roche, Amgen, PharmaMar and has been part of advisory boards of Tesaro, Amgen and PharmaMar, outside the submitted work. Dr.Pignata reports honoraria from AstraZeneca, Tesaro Clovis, Roche,Pharmamar, MSD, Pfizer and Research funding from AstraZeneca, MSD, Roche Pfizer outside the submitted work.Dr. Arenare, Dr.Ronzino, Dr. Lauria, Dr. Cormio, Dr.Carella, Dr. Scollo, Dr. Ghizzoni, Dr. Raspagliesi, Dr. Di Napoli,Dr. Mazzoni, Dr. Marchetti, Dr. Scambia, Dr. Maltese, Dr. De Matteis, Dr Cardalesi, Dr. Loizzi, Dr. Boccia, Dr. Naglieri and Dr. Scandurra have nothing to disclose.

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347 **Table 1**: patients characteristics at diagnosis of ovarian cancer

Characteristic of patients	**N=234 (%)**	
Age ,years		
Median, IQR	53.2	(46.6-59.4)
ECOG PS, n (%)		
0	167	(71.4)
1	48	(20.5)
2	10	(4.3)
Unknowm	9	(3.8)
Comorbidities, n (%)		
Yes	90	(38.5)
No	123	(52.5)
Unknown	21	(9.0)
Familiar history for Breast or Ovarian cancer, n (%)		
Yes	100	(42.7)
No	118	(50.4)
Unknown	16	(6.8)
Personal history of Breast cancer, n (%)		
Yes	36	(15.4)
No	179	(76.5)
Unknown	19	(8.1)
BRCA status, n (%)		
BRCA 1 mutation	163	(69.7)
BRCA 2 mutation	70	(29.9)
BRCA 1 and BRCA 2 mutation	1	(0.4)
Type of mutation, n (%)		
Germline	153	(65.4)
Somatic	14	(6.0)

Unknown	67	(28.6)
Stage (FIGO) at diagnosis, n (%)		
I-II	27	(11.5)
III	176	(75.2)
IV	25	(10.7)
Unknown	6	(2.6)
Histology, n (%)		
Serous	215	(91.9)
Endometrioid	14	(6.0)
Clear cell	2	(0.9)
Mixed	1	(0.4)
Transitional	2	(0.9)
Residual, n (%)		
None	141	(60.3)
≤ 1 cm	41	(17.5)
> 1 cm	41	(17.5)
Unknown	11	(4.7)
Fist line treatment, n (%)		
Carboplatin- Paclitaxel three weekly+ Bevacizumab	97	(41.5)
Carboplatin Single agent	2	(0.9)
Carboplatin- Paclitaxel three weekly	113	(48.3)
Carbopltin Paclitaxel weekly	17	(7.3)
Others	5	(2.1)
PFI after first line,months		
Median, IQR	18.0	(12.0-27.5)

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350 **Table 2**: patients characteristics at time of olaparib administration

Characteristic of patients	**N=234**	**(%)**
Number of platinum based lines pre olaparib		
2	111	(47.4)
3-4	96	(41)
>4	27	(11.5)
PFI before last platinum based therapy(months)		
Median, IQR	9	(5-14.2)
Platinum based therapy before olaparib		
Platinum combo	202	(86.3)
Platinum single agent	24	(10.3)
Other	8	(3.4)
Radiologic response to last platinum based therapy		
Complete response	91	(38.9)
Partial response	106	(45.3)
Stable Disease	29	(12.4)
Progressive disease	1	(0.4)
Unknown	7	(3.0)
Ca125 before olaparib administration		
≤35 UI/ml	138	(59.0)
>35 UI/ml	51	(21.8)
Unknown	45	(19.2)

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352 **Table 3: :** Exploratory subgroup analysis of Progression-free Survival

	HR	p	95%CI
Ca 125			
Low vs high	2.5	0.001	1.5-4-3
Number of previous lines			
1 vs 2 previous lines	1.9	0.031	1.1-3.5
1 vs >2 previous lines	2.5	0.004	1.3-4.8
RECIST response to last platinum based therapy			
CR vs PR	3.1	0.001	1.6-5.8
CR vs SD or PD	2.7	0.017	1.2-6.1
FIGO Stage at diagnosis			
I-II vs III	1.0	0.11	0.5-2.3
I-II vs IV	1.1	0.25	0.4-3-0
Residual disease			
R=0 vs R≠0	1.5	0.117	0.9-2.4
Previous treatment with bevacizumab			
Yes vs not	1.15	0.641	0.6-2.1
BRCA status			
BRCA1 vs BRCA2 mutation	0.7	0.165	0.4-1.2
Age			
Old vs young	1	0.169	1.0-1.0
ECOG PS			
0 vs 1	1.6	0.139	0.9-3.0
0 vs 2	1.6	0.289	0.6-4.0

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355 **Table 4**: recorded G3-G4 AEs

Adverse event G3-G4	N=234	(%)
Nausea	8	(3.4)
Fatigue	3	(1.3)
Anemia	13	(5.6)
Thrombocytopenia	5	(2.1)
Leucopenia or Neutropenia	4	(1.7)
Abdominalpain	1	(0.4)
Vomiting	2	(0.9)
MDS	1	(0.4)
Hypomagnesaemia	1	(0.4)

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366 **Table 5**: Response to chemotherapy in patients treated after progression to olaparib.

Platinum free interval	**CR**	**PR**	**SD**	**PD**
PFI< 6mm	1 (4.8)	1(4.8)	3 (14.3)	16 (76.2)
PFI: 6-12 mm	0	3 (11.1)	8 (29.6)	16 (59.3)
PFI >12 mm	1 (5.6)	3 (16.7)	7 (38.9)	7 (38.9)

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Table 6:table comparing results from SOLO2 Trial and this real world study.

	SOLO2	MITO Real life study
PFS	19.1 months	14.7 months
ORR	30 (41.1%)	57(46.3%)
Dose reduction	49 (25%)	49 (20.9%)
Dose discontinuation	21 (11%)	11 (4.7%)

Figure 1: With a median follow up of 15.5 months (95% CI 13.0-18.2), median PFS was 14.7 months (Figure 1a) while median OS was not reached (Figure 1b).

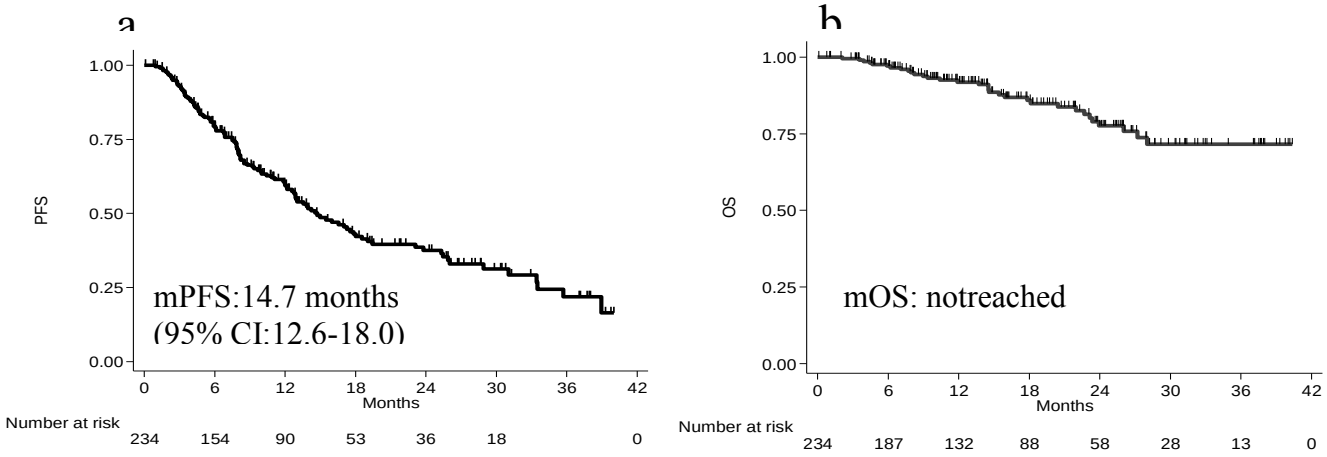
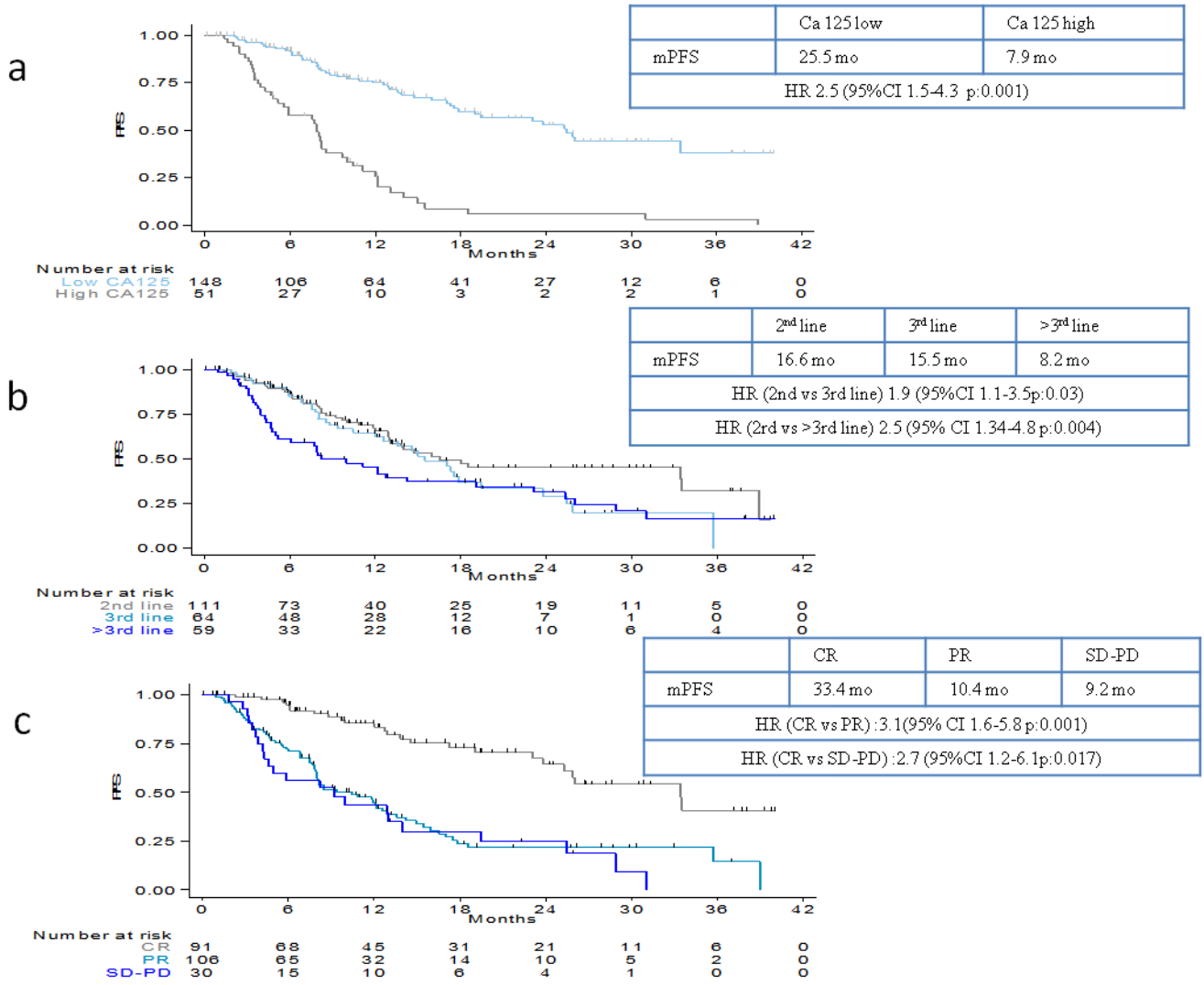


Figure 2: Median PFS according to serum Ca125 at baseline (cut off 35 UI/ml, Figure 2a), number of previous platinum based lines (Figure 2b) and response to last platinum based therapy (Figure 2c).



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